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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,241	06/12/2006	Napoleone Ferrara	11669.0162USWO	5101

23552 7590 12/03/2008

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,241	FERRARA ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/11/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72,74-76,78-81,83-85,102-121 and 123-128* is/are pending in the application.

4a) Of the above claim(s) *102-121* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72,74-76,83-85 and 123-128* is/are rejected.

7)☒ Claim(s) *78-81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/2007,08/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 08/11/2008 have been entered in full. Claims 1-71, 73, 77, 82, 86-101 and 122 are cancelled. Claims 102-121 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 72, 74-76, 78-81, 83-85, and 123-128 are under examination.

2. A signed copy of the IDS filed 11/30/2007 is included with this office action to indicate that the previously missing reference by Lin *et al.* has been received and considered.

3. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn. The following is noted with regard to withdrawal of the rejection of claims 72-83, 85-99, 101 and 122 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants have canceled claims 77 and 82 and amended claim 72 to include recitation of percent identity limitations relative to identified sequences. The amendment also removed the function limitation "and induces proliferation of endothelial cells", which had been in the original claims. Applicants are advised that it is this latter amendment, and not Applicants' argument filed 08/11/2008, that prompts the withdrawal of the rejection. The Examiner relies on the revised Written Description Training Materials, published on March 25, 2008, available at www.uspto.gov/web/menu/written.pdf, particularly Examples 11A and 11B, wherein it is shown that the inclusion of a functional limitation drastically alters the analysis of a claim reciting percent identity to an identified sequence. Portions of Applicants' argument filed 08/11/2008 will be cited as they relate to a new rejection under 35 U.S.C. 112, first paragraph, set forth herein.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Rejection of Claims 72, 74-76 and 83-85 under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication 20030027998, is maintained and hereby extended to include new claims and 123, 124, 126, and 127. Applicant's arguments filed 08/11/2008 have been fully considered but they are not persuasive. As previously noted, the '998 publication discloses a polypeptide designated TANGO 266, SEQ ID NO:64. This disclosed polypeptide is identical to SEQ ID NO:8 (EG-VEGF) of the instant application. Applicant argues that the '998 publication does not disclose contacting lymphoid lineage progenitor cells or progeny thereof with EG-VEGF or that EG-VEGF is capable of inducing the proliferation of lymphoid lineage progenitor cells or progeny thereof. This is not persuasive because the '998 publication discloses contacting bone marrow mononuclear cells with TANGO 266; a mitogenic response was observed [1005-1007]. This cell population inherently contains lymphoid lineage progenitor cells and lymphoid precursor cells as recited in instant claims 72 and 74. The prior art need not have recognized that EG-VEGF is capable of inducing the proliferation of lymphoid lineage progenitor cells or progeny thereof, such result would be

inherent in contacting the same cells with the same agent. It is noted, however, that a mitogenic response was observed and there is no evidence that this response was confined the myeloid cells that received further characterization in the '998 publication. Furthermore, the prior art did recognize the proliferative effect on all lymphoid cells. The '998 publication discloses hematopoietic progenitor cells transduced with a vector to express TANGO 266; the transduced cells were transplanted into sublethally irradiated C57B16 mice and allowed to reconstitute the hematopoietic system [1012-1013]. This method would lead to contacting all lymphoid cells recited in the instant claims. Since reconstitution of the hematopoietic system would include increasing all kinds of white blood cells, including both T and B cells, this anticipates the method recited in claims 123, 124, 126, and 127, wherein EG-VEGF/TANGO 266 is administered to a subject following radiation. The '998 publication recognized the ability of EG-VEGF/TANGO 266 to induce the proliferation and differentiation of white blood cell types [1027-1028], and specifically teaches T and B lymphocytes as targets of action [1032]. The '998 publication teaches recipients of myelotoxic and immunosuppressive drugs [1031] (as in claims 123 and 126) as among the patient population for administration of EG-VEGF/TANGO 266.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 125 and 128 rejected under 35 U.S.C. 103(a) as being unpatentable over Patent Application Publication 20030027998 as applied to claims 123, 124, 126, and 127 above, and further in view of US 20030171306, filed June 4, 2001. As noted, the '998 publication anticipates claims 123 and 126 by teaching the administration of EG-VEGF/TANGO 266 for increasing all kinds of white blood cells, including both T and B cells, in recipients of myelotoxic and immunosuppressive drugs. The '998 publication, however, did not specifically name any myelotoxic or immunosuppressive drugs as recited in claims 125 and 128. Without any additional teaching, one of skill in the art would have a reasonable expectation of success in applying the general approach taught in the '998 application in patients that have been treated with any known myelotoxic or immunosuppressive agent. The purpose of such treatment is to reduce unwanted side-effects of cancer chemotherapy, which is well known in the art to be toxic to bone marrow, which leads to a reduction in both white and red blood cells and immunosuppression (see US 20030171306 at [0002-0003]). US 20030171306 discloses the use of many of the same cancer chemotherapeutic agents recited in claims 125 and 128 to demonstrate a different approach to alleviating these myelotoxic or immunosuppressive effects. See, for example, Figures 2-8, paragraphs [0042-0052] and Table 1, which at least include teaching of 5-fluorouracil, vincristine, cisplatin, methotrexate, paclitaxel, and doxorubicin (an anthracycline). US 20030171306 shows that the agents recited in claims 125 and 128 are in the genus of myelotoxic and immunosuppressive drugs taught in the '998 application, and that there is a recognized need for agents such as EG-VEGF/TANGO 266 for promoting recovery in patients that have been treated with these

agents. US 20030171306, therefore, further reinforces the motivation and expectation of success already provided in the '998 application for administering EG-VEGF/TANGO 266 as recited in instant claims 125 and 128.

New Objections and Rejections

Sequence Compliance

8. 37 C.F.R. 1.821 provides that any unbranched sequence of four or more amino acids must be identified by a sequence identifier (SEQ ID NO.), and listed in the sequence listing. 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Figure 7 depicts an amino acid sequence, labeled as Mouse Bv8, which does not appear in the Sequence Listing for this application. Applicant is required to submit a new sequence listing and make appropriate amendments to the specification and claims in order to bring the case into compliance.

Drawings

9. Figure 7 is objected to because the sequence depicted for mouse long form Bv8 is not supported by a sequence identifier (SEQ ID NO). Furthermore, the depicted sequence is at odds with the remainder of the disclosure. In particular, the amino acids immediately C-terminal to the heparin binding domain are shown as VVPF. Figure 6, which shows the sequence of the short form of mouse Bv8, depicts the sequence VPF in the corresponding

position, as does SEQ ID NO:6. Therefore, Figure 7 has an extra V relative to the other disclosures. It is not clear that this is a mistake, as no sequence for mouse long form Bv8 is found in the sequence listing for this application. This discrepancy leads to a lack of clarity as to the extent of identity between the sequences depicted in Figure 7, which in turn is relevant to the guidance provided with respect to sequence variants. If Applicants can persuasively argue that this was a mistake, it may be corrected if the correct sequence of mouse long form Bv8 can be can be entered into the disclosure from a source that has already been incorporated by reference.

10. A corrected drawing sheet in compliance with 37 CFR 1.121(d) is required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 72, 74-76, 78-81, and 123-128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising contacting cells with a Bv8 polypeptide comprising at least 90% identity the amino acid sequence of SEQ ID NO:2, or SEQ ID NO:4, does not reasonably provide enablement for methods comprising contacting cells with a Bv8 polypeptide comprising at least 80% identity to SEQ ID NOs: 2 or 4, as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

13. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement

requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

14. *The nature of the invention:* The claims are drawn to methods inducing proliferation of lymphoid lineage progenitor cells, or progeny thereof, comprising contacting said cells with Bv8 or EG-VEGF polypeptides characterized by a percentage of amino acid sequence identity to disclosed sequences identified by SEQ ID NOs: 2 or 4.

15. *The breadth of the claims*: The genus of polypeptides recited for use in the methods is enormous. For example, the number of polypeptides that are 80% identical to SEQ ID NO:4, which comprises 108 amino acids, is greater than 7.5×10^{50}. The corresponding number for SEQ ID NO:2, which comprises 129 amino acids, would be still higher. Furthermore, claim 78 recites *an* amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, or SEQ ID NOs:6. This recitation does not limit to an entire sequence, the indefinite article 'an' (as opposed to 'the') indicates that the limitation could be met by any two consecutive amino acids from within the recited sequences.

16. *The state of the prior art and the predictability or lack thereof in the art:* The art teaches that the effect of amino acid substitution in a peptide or protein, is unpredictable and can produce

an effect opposite to that which is desired. While many examples wherein small changes in amino acid sequence result in profound changes in activity could be cited, the findings of Ju *et al.* (Proc Nat'l Acad Sci U S A. 1991 Apr 1;88(7):2658-62) and Kruse *et al.* (EMBO J. 1992 Sep;11(9):3237-44) are particularly pertinent to the instant case as the recited methods require activation of growth factor receptors. Ju *et al.* found that a single amino acid substitution could change IL-1ra from an antagonist to a partial agonist. Kruse *et al.* reported that IL-4 can be changed from agonist to antagonist by a single amino acid change. It follows that the significance of particular amino acids and sequences for the biological activity of peptide growth factors cannot be predicted *a priori* but must be experimentally determined from case to case.

17. The art recognizes that conserved structural features among Bv8 from different species such as human, rat mouse, snake, and frog were known. Characteristic features of the family of Bv8 proteins include the N-terminal AVIT sequence and the 10 cysteines with identical spacing in the C- terminal domain (Kaser et al., 2003, EMBO Reports, 4:469-473; of record). The N- terminal AVIT sequence was known to be necessary for biological activity. For example, deletion of the AVIT sequence was known to result in Bv8 variants that were able to bind to prokineticin receptors but unable to activate the receptors (Negri et al., 2005, Brit. J. Pharmacol., 146:625-632; of record). Similarly, the art recognizes that EG-VEGF comprises a N-terminal AVIT sequence and the 10 Cys with identical spacing in the C-terminal domain.

18. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the

art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification teaches that the long and short forms of Bv8 differ by the presence or absence of a 21 amino acid potential heparin binding domain, which is determined by alternative splicing of the encoding mRNA ([0030], FIG. 7). SEQ ID NO:2 is the 129 amino acid sequence of the human long form and SEQ ID NO:4 is the 108 amino acid sequence of the human short form. Since the short form, SEQ ID NO: 4, is held to be active in the recited methods, it follows that the heparin binding domain is dispensable. Also, the 21 amino acid signal peptides of the respective proteins are not present in the mature proteins or required for activity. SEQ ID NO:2 includes the heparin binding domain and both SEQ ID NO:2 and SEQ ID NO:4 include the signal peptide. These must be taken into account in considering the guidance in the specification as to how much sequence variability can be tolerated while retaining activity.

19. The mature short form, lacking the signal peptide, retains only 87 of the 108 amino acids of SEQ ID NO:4. 87/108= 80.6 %. This appears to be the basis for the 79% identity figure cited in Applicant's arguments filed 08/11/2008, p.9. The 79% is actually 80.6%, and it was calculated by comparing short forms which have no heparin binding domain. The percentage reflects the removal of the signal peptide, not a difference among the 87 amino acids that are common to both the mature long and short forms. Likewise, the assertion that human long and short forms are only 79% (actually 80.6%) identical (Applicant's arguments filed 08/11/2008, p.9) does not mean that the disclosure of these two forms establishes that Bv8 may vary by 20% identity and still be active—the two forms are identical outside of the dispensable heparin binding domain and the signal peptide that is not present in the mature active proteins. The recited 80% sequence identity limitations for Bv8 are supported only if

the deviations from the reference sequence are confined to the 21 amino acid signal peptide and the 21 amino acid heparin binding domain. 80% sequence identity to either SEQ ID NO:2 or SEQ ID NO:4 is not supported.

20. Given that the signal peptide and the heparin binding domain are dispensable for activity, this leaves 87 amino acids from the 129 amino acid full length translation product of human Bv8 (SEQ ID NO:2). The specification does not provide guidance as to how these may be varied, and indeed suggests that little deviation is tolerated. Applicant has asserted that "Outside of the heparin binding domain, the short and long forms of human, mouse, and rat Bv8 only differ by 4 amino acids and have 10 conserved cysteines" (arguments filed 08/11/2008, p.9). This conclusion is at odds with the specification at Figure 7, which shows that the difference between human and mouse long forms is 6 amino acids in the mature protein (substitutions at positions 64,65, 96, 97, 128, and an insertion in mouse relative to human at position 99; differences in the 21 amino acid signal peptide not counted). Nevertheless, assuming that Applicants' assertion of only 4 differences is correct, human and mouse Dv8 sequences differ at 4 of 87 positions, or about 4.6 %, excluding the heparin binding domain and the signal sequences. This appears to be the basis whereby the specification teaches that the mouse and human Bv8 homologues are approximately 96% identical [0030]). This is true only if the short forms are compared, thereby excluding the heparin binding domain, and signal sequences are excluded. Over the full 129 amino acids of the long form (SEQ ID NO:2) the actual identity is about 88%. Over the full 108 amino acids of the short form (SEQ ID NO:4) the actual identity is about 92%. (These are calculated by visually counting the differences in the sequences in Figure 7 with the assumption of an error at position 97. As Figure 7 relies

on a mouse sequence that is not identified by a sequence identifier or listed in the sequence listing, this sequence could not be searched, and it would not be returned in searches that use related sequences as the query sequence. Therefore, the alignment, calculated query match, and percent similarity that would be obtained in a USPTO STIC sequence search are not available). Therefore, the disclosure of sequence variability among Bv8 polypeptides from different mammalian species does not support a prediction that polypeptides with as little as 80% identity to SEQ ID NO:2 or SEQ ID NO:4 will be active, nor does it provide guidance for the making and using of such diverse polypeptides.

21. *The quantity of experimentation needed:* While great numbers of sequences may be described and recognized with the aid of a computer, it is another matter to make and use all of them in methods that require the activity of receptor binding and activation, which is known to be sensitive to small variations in structure. Therefore, it would require undue experimentation for one of skill in the art to make and use the claimed invention in its full scope.

Conclusion

22. Claims 72, 74-76, 83-85, and 123-128 are rejected.

23. Claims 78-81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/

Examiner, Art Unit 1647